WHAT IS CLAIMED IS:

1. A method for targeting a therapeutic agent to a target site in a patient, comprising the steps of:

(a) administering to the patient an effective amount for targeting of at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, administering to the patient an amount effective for clearance of a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) administering to the patient an effective amount for enzyme activity of the enzyme, such that the targeting protein binds the enzyme to form a targeting protein-enzyme conjugate *in situ*;

(d) optionally, administering to the patient an amount effective for clearance of a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation;

(e) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme administered in step (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out at the target site such that it accretes at the

target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

2. The method of claim 1, wherein the targeting protein comprises a conjugate of at least one antibody, antibody fragment, or antibody subfragment which provides the first binding site and at least one antibody, antibody fragment or antibody subfragment which provides the second binding site.

3. The method of claim 1, wherein the targeting protein comprises a fusion protein comprising the first and second binding sites.

4. The method of claim 1, wherein the targeting protein comprises a covalent conjugate of at least two single chain antibodies, wherein at least one single chain antibody provides the first binding site and at least one single chain antibody provides the second binding site.

5. The method of claim 1, wherein the enzyme is selected from the group consisting of esterases, proteases, glucuronidases, dextranases, cellulases, and glycosidases.

6. The method of claim 5, wherein the enzyme comprises carboxyesterase.

7. The method of claim 5, wherein the enzyme comprises an esterase and the prodrug comprises CPT-11.

8. The method of claim 5, wherein the enzyme comprises beta-glucuronidase and the prodrug comprises CPT-11.

9. The method of claim 5, wherein the targeting protein comprises a conjugate of hMN-14 and anti-human-beta-glucuronidase, and the enzyme comprises human-beta-glucuronidase.

10. The method of claim 5, wherein the second binding site of the targeting protein is specific for DTPA, and the enzyme comprises a DTPA-human-beta-glucuronidase conjugate.

11. The method of claim 5, wherein the enzyme is selected from the group consisting of dextranases and cellulases, and wherein the prodrug comprises an aminodextran or polylysine carrier that is not acted on by the enzyme, to which is conjugated at least one molecule or ion of therapeutic agent, and which is further conjugated to at least one solubilizing dextran or carboxymethylcellulose oligomer which is acted on by the enzyme.

12. The method of claim 1, wherein the enzyme is selected from the group consisting of alkaline phosphatase, beta-lactamase, and carboxypeptidase G2.

13. The method of claim 12, wherein the enzyme comprises carboxypeptidase G2 and the prodrug comprises CPT-11.

14. The method of claim 1, wherein the prodrug is a low molecular weight compound, with a molecular weight below about 50 KDa.

15. The method of claim 14, wherein the prodrug comprises a benzoic or phenolic or anilic derivative of mustard.

16. The method of claim 1, wherein the prodrug comprises a glucuronide conjugate of the therapeutic agent.

17. The method of claim 1, wherein the prodrug comprises a polymer.

18. The method of claim 17, wherein the polymer is a dextran, an aminodextran, a carboxymethylcellulose or a polypeptide.

19. The method of claim 17, wherein the prodrug comprises a polyethylene glycol (PEG) molecule conjugated at both its free hydroxyl ends to one molecule or ion of the therapeutic agent.

20. The method of claim 17, wherein the polymer is conjugated to the therapeutic agent via a peptide linker.

21. The method of claim 20, wherein the peptide linker is cleaved by a cathepsin, and wherein the enzyme comprises a cathepsin.

22. The method of claim 17, ~~wherein the~~ prodrug comprises a ~~polymer~~ that is not acted on by the enzyme to

which is attached at least one oligomer to which is conjugated at least one molecule or ion of therapeutic agent, wherein the oligomer is acted on by the enzyme.

23. The method of claim 1, wherein the targeting protein comprises at least two first binding sites which specifically bind to the same or different epitopes of the same or different substance produced by or associated with the target site and present at the target site.

24. The method of claim 1, wherein step (a) comprises administering at least two different targeting proteins each of which comprise a first binding site which specifically binds to a different substance produced by or associated with the target site and present at the target site.

25. The method of claim 1, wherein the targeting protein comprises at least two second binding sites which specifically bind to different enzymes, and wherein step (c) comprises administering the different enzymes.

26. The method of claim 1, wherein step (a) comprises administering at least two different targeting proteins each of which comprise a second binding site which specifically binds to a different enzyme, and wherein step (c) comprises administering the different enzymes.

27. The method of claim 26, wherein step (c) results in the *in situ* formation of a targeting protein-enzyme conjugate comprising carboxypeptidase G2 and a

targeting protein-enzyme conjugate comprising glucuronidase.

28. The method according to claim 27, wherein the prodrug comprises CPT-11.

29. The method of claim 26, wherein step (c) results in the *in situ* formation of a targeting protein-enzyme conjugate comprising esterase and a targeting protein-enzyme conjugate comprising glucuronidase.

30. The method according to claim 29, wherein the prodrug comprises CPT-11.

31. The method of claim 1, wherein the targeting protein, the enzyme, or both, is labeled with a detectable label such that step (c) results in the *in situ* formation of a labeled targeting protein-enzyme conjugate, and the method further comprises, prior to step (e), detecting the detectable label to determine the location of the targeting protein-enzyme conjugate.

32. The method of claim 31, wherein the detectable label is selected from the group consisting of radioisotopes and magnetic resonance image enhancing agents.

33. The method of claim 1, wherein the targeting protein, the enzyme, or both, comprises a therapeutic agent such that step (c) results in the *in situ* formation of a targeting protein-enzyme conjugate comprising a therapeutic agent.

34. The method of claim 33, wherein the therapeutic agent of the targeting protein-enzyme conjugate is selected from the group consisting of radionuclides, drugs, toxins, and boron addends.

35. The method of claim 33, wherein the therapeutic agent of the targeting protein-enzyme conjugate is a radionuclide selected from the group consisting of I-131, I-125 and At-211.

36. The method of claim 1, wherein the optional clearing composition of step (b) is administered.

37. The method of claim 36, wherein the clearing agent is anti-idiotypic to a first binding site of the targeting protein.

38. The method of claim 37, wherein the clearing agent is an anti-idiotypic monoclonal antibody.

39. The method of claim 36, wherein the clearing agent is modified with a number of sugar residues sufficient to effect hepatic clearance substantially in a single pass.

40. The method of claim 39, wherein at least about 48% of the lysine residues of the clearing agent are modified with sugar residues.

41. The method of claim 40, wherein at least about 76% of the lysine residues of the clearing agent are modified with sugar residues.

42. The method of claim 1, wherein the therapeutic agent comprises a boron addend, and the method further comprises, after step (e), irradiating the boron.

43. The method of claim 42, wherein the boron addend is labeled with a detectable label and the method further comprises, prior to the step of irradiating the boron, detecting the detectable label to determine the location of the boron addend.

44. The method of claim 1, wherein the therapeutic agent is a beta- or alpha-emitting radioisotope, a drug, a toxin, a boron addend, a vasodilator, a cytokine, a photosensitizer or a radiosensitizer.

45. The method of claim 1, wherein the prodrug is CPT-11 and the therapeutic agent is camptothecin.

46. The method of claim 1, wherein the target site is selected from the group consisting of tumors, infectious lesions, parasitic lesions, fibrin clots, myocardial infarctions, atherosclerotic plaques, non-cancerous cells and damaged normal cells.

47. The method of claim 1, wherein the first binding site specifically binds to a cancer marker selected from the group consisting of MUC1, sTn, Le(y), PMSA, Her2/neu, CD20, GM2 and GD3.

48. The method of claim 1, wherein the first binding site specifically binds to a cancer marker selected from the group consisting of CSAp and DNA histone.

49. The method of claim 1, wherein the compositions are administered by an intracavitary, intravenous, intraarterial, intrapleural, intrathecal, intralymphatic, intramuscular, intralesional, subcutaneous or catheter perfusion route.

50. The method of claim 1, wherein the patient is a human.

51. A kit for targeting a therapeutic agent to a target site in a patient, comprising, in separate containers:

(a) at least one multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) the enzyme;

(d) optionally, a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation; and

(e) a serum-soluble prodrug composition, wherein the enzyme of component (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out

at the target site such that it accretes at the target site to a greater extent than would the prodrug.

52. A sterile injectable preparation for targeting a therapeutic agent to a target site in a patient, comprising:

(a) at least one first sterile injectable solution comprising a multispecific targeting protein comprising at least one first binding site which specifically binds to a substance produced by or associated with the target site and present at the target site and at least one second binding site which specifically binds to an epitope on an enzyme, wherein binding between the targeting protein and the enzyme does not interfere with enzyme activity;

(b) optionally, a second sterile injectable solution comprising a first clearing composition comprising a clearing agent which clears non-localized targeting protein from circulation;

(c) a third sterile injectable preparation comprising the enzyme;

(d) optionally, a fourth sterile injectable preparation comprising a second clearing composition comprising a clearing agent which clears non-localized targeting protein, non-localized enzyme, or non-localized targeting protein-enzyme conjugate from circulation; and

(e) a fifth sterile injectable preparation comprising a serum-soluble prodrug composition, wherein the enzyme of preparation (c) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out at the target site such that it accretes

at the target site to a greater extent than would the prodrug.

53. A method for targeting a therapeutic agent to a target site in a patient, comprising:

(a) administering to the patient at least one targeting composition comprising at least one targeting protein-enzyme conjugate comprising a binding site which specifically binds to a substance produced by or associated with the target site and present at the target site, and allowing the conjugate to localize at the target site;

(b) optionally, administering to the patient a clearing composition comprising a clearing agent which clears non-localized targeting protein-enzyme conjugate from circulation; and

(c) administering to the patient at least one serum-soluble prodrug composition, wherein the enzyme of the targeting protein-enzyme conjugate administered in step (a) acts on the prodrug to release a therapeutic agent that is less soluble in serum than the prodrug, and wherein the therapeutic agent partitions out at the target site such that it accretes at the target site to a greater extent than would the prodrug, thereby providing therapeutic agent at the target site.

54. The method of claim 53, wherein the targeting protein-enzyme conjugate comprises a fusion protein of the targeting protein and the enzyme.